



REMARKS

**The Claims Are Not Rendered Obvious by Rockwell in View of Ciardiello**

Claims 1-6, 9, 11-14, 16-18, 28, 62, and 67-69 stand rejected under 35 U.S.C. 103(a) as being allegedly rendered obvious by Rockwell in view of Ciardiello. Applicants traverse this rejection.

Ciardiello describes administering a combination of a VEGF antisense oligonucleotide and an EGFR antibody to potentially inhibit tumor growth.<sup>1</sup> Rockwell makes no mention of VEGF antisense but rather describes VEGFR antibodies. Applicants submit that one skilled in the art would not be motivated to substitute the VEGF antisense described by Ciardiello with a VEGFR antibody as described by Rockwell for at least the following reasons.

First, because Ciardiello describes a VEGF antisense oligonucleotide, Ciardiello is directed to inhibiting VEGF expression and eliminating the protein entirely. Therefore, Ciardiello describes preventing VEGF production by tumor cells such that VEGF is not even available to bind to the different VEGF receptors expressed on endothelial cells to thereby activate angiogenesis. Rockwell, on the other hand, describes inhibiting VEGF further downstream, i.e. inhibiting (once produced by tumor cells) the interaction between VEGF with the VEGF receptors expressed on endothelium cells to inhibit angiogenesis (See Figure 4). However, Rockwell indicates that "VEGF mediates its regulatory response on endothelial cells through two high-affinity PRK receptors, mouse flk-1 and its human homologs KDR and a second receptor, flt-1" (See page 321). One skilled in the art would not be motivated to use VEGFR antibodies instead of VEGF antisense because antibodies to both flk-1 and flt-1 may be required to get the same results as a VEGF antisense. In other words, there is no motivation to change a single VEGF knockout approach with an approach that requires antibodies to two different receptors.

Further, as of the filing date of the present application, it was known that neuropilin-1, which binds to VEGF, also mediates angiogenesis via its interaction with VEGF. (See Exhibit A). Therefore, to one skilled in the art considering Rockwell and Ciardiello in view of the general knowledge in the art regarding VEGFR receptors that mediate angiogenesis,

<sup>1</sup> Applicants wish to clarify that there was never an acknowledgment in any previously filed response that Ciardiello showed a synergistic effect upon administering an antisense VEGF oligonucleotide with an EGFR antibody.

binding of VEGF to three different receptors may need to be blocked in order to get the same result as a single VEGF antisense. It is Applicants' position that such a multi-receptor approach undercuts any motivation to replace the VEGF antisense described by Ciardiello with a VEGFR antibody described by Rockwell.

Second, Ciardiello describes using two approaches, VEGF antisense and C225, that both involve reducing the source of VEGF from tumor cells. Namely, VEGF anti-sense inhibits the synthesis of VEGF and C225 inhibits the secretion of VEGF (See Ciardiello page 3742, second column). Ciardiello mentions in the introduction that an anti-VEGF antibody has been generated and that the development of antibodies against the VEGF-specific flk-1/KDR is "a promising approach." Therefore, although Ciardiello recognizes two approaches that target VEGF after VEGF is produced by tumor cells, Ciardiello pursues a dual approach to reducing VEGF from even being produced by tumor cells in the first place. Applicants submit that to one skilled in the art, such a direction of Ciardiello suggests or points to therapeutic approaches that are directed to reducing the source of VEGF. Rockwell, on the other hand, describes antibodies that bind to VEGFR and inhibit binding of VEGF to its receptor and that do not target the production of VEGF.

For at least these reasons, Applicants submit that there is no motivation to combine Rockwell with Ciardiello and therefore these references do not render obvious the present claims. Accordingly, Applicants request withdrawal of this rejection.

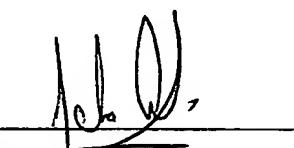
**CONCLUSION**

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Any fees for extension(s) of time or additional fees required in connection with the filing of this response, are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is authorized to charge any such required fees or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,  
KENYON & KENYON LLP

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